Remarks

This Amendment is responsive to the Office Action of April 25, 2003. Entry of this Amendment and reconsideration of the subject application in view thereof are respectfully requested.

I. Claims

Claims 40-42 were pending in the application and these claims stood rejected.

Claim 40 has been amended to clearly define the invention. Support for the recitation "lasting for more than one hair cycle and leading to development of dark pigmented hairs" can be found in the specification, for example, at page 14 lines 5-18. Support for the new claims 43-53 can be found, for example, at page 47 line 30 through page 48, line 29 of the disclosure. Applicant respectfully submits that no new matter is added by these amendments.

II. Rejections Under 35 U.S.C. §103

Claims 40-42 stood rejected as allegedly being obvious over Yoon et al., 1996, Proc. Natl. Acad. Sci., 93:2071-2076 and Alexeev et al., 1998, Nature Biotechnology 16:1343-1346, Furth et al., U.S. Patent 5,998,382 in view of Gilchrest et al., U.S. Patent 5,580,547 and Stout et al., 6,319,224. Applicant respectfully traverses this rejection.

The Examiner avers that the Yoon and Alexeev references demonstrate the feasibility of RNA-DNA oligonucleotide mediated correction of gene mutations in *in vitro* cultured cells, Furth, Gilchrest and Stout provide specific methodology for the delivery of a polynucleotide to the skin and, therefore, the claimed invention is obvious. Applicant respectfully disagrees.

Contrary to what the Examiner appears to be urging, *prima facie* obviousness has not been established in this case. A proper analysis under §103 requires, among other things, consideration of (1) whether the prior art would have suggested to those of ordinary skill in the art that they should carry out the claimed process; and (2) whether the prior art would also have revealed a reasonable expectation of success in carrying out the process. *See In re Vaeck,* 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success

must be founded in the prior art, not in the applicant's disclosure. *Id*; *In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998).

Yoon et al. teaches modifications of a gene on a plasmid in chinese hamster ovary cells (host cells) *in vitro* using a chimeric RNA-DNA oligonucleotide. Alexeev relates to gene modifications in isolated and cultured melan-c cells using a Tyr-A RNA-DNA oligonucleotide. Alexeev, reports gene modifications with a frequency range of 0.01-15%. Furth, Gilchrest and Stout relate to DNA delivery into a mammalian skin.

The cited combination of references simply does not disclose or suggest a method of correcting a mutation in a tyrosinase gene in cells of a mammalian skin in vivo. More particularly, there is no suggestion either in Yoon or in Alexeev cited against all claims, of correcting a mutation in a tyrosinase gene in cells at one or more locations of a mammalian skin in vivo using a Tyr-A RNA-DNA oligonucleotide such that the correction results in restoration of tyrosinase enzyme activity lasting for more than one hair cycle and leading to the development of pigmented hairs at said locations of the mammalian skin. Neither Yoon nor Alexeev provides any suggestion as to what parameters are needed or not needed for stable tyrosinase gene correction by a Tyr-A RNA-DNA oligonucleotide at the genomic and phenotypic levels *in vivo* as claimed. As to Furth, Gilchrest and Stout, Applicant respectfully submits that the present invention is not specifically directed to a specific methodology for delivering DNA into mammalian skin; rather, the specific elements of Applicant's claimed invention are at issue. These references suggest nothing about how to correct a mutation in the tyrosinase gene in skin. For that matter, there is nothing in the Furth, Gilchrest and Stout references about correcting a mutation in a skin gene by using any RDO so that one can arrive at the claimed invention by combining these references with the Yoon and Alexeev references.

Applicant respectfully submits that the teachings related to correction of episomal genes in chinese hamster ovary cells, or correction of tyrosinase gene in isolated melan-c cells or methods of delivery of DNA to skin, without more, do not provide a suggestion or motivation to one skilled in the art to arrive at the claimed invention. Nowhere does Yoon or Alexeev, (e.g., page 1343 of Alexeev or page 2076 of Yoon pointed to by the Examiner on pages 4-5 of the Office Action) provide suggestion or motivation as to how to correct a mutation in a tyrosinase

gene in cells of a mammalian skin in vivo so that one can arrive at the claimed invention. Furth, Gilchrest and Stout references fail to remedy these deficiencies. Stated otherwise, even when Furth, Gilchrest and Stout are combined, which references teach certain DNA delivery methods, with the Yoon and Alexeev references one cannot arrive at the claimed invention because Furth, Gilchrest and Stout references do not cure the deficiencies in the Yoon and Alexeev references.

The cited references, at most, are invitations to try[1] Tyr-A RNA-DNA oligonucleotide mediated modification of tyrosinase gene in melanocytes in skin but do not provide a suggestion or motivation to one of ordinary skill in the art as to how to cause a stable genetic correction in the tyrosinase gene in a skin cell such that the correction results in the restoration of tyrosinase enzyme activity leading to development of pigmented hairs and lasting for more than one hair cycle at a given location of a mammalian skin. In other words, the cited references may pique the curiosity of one skilled in the art such that further investigation might be done as a result, but the references themselves do not contain sufficient teachings of how to obtain the end result or that stable genetic correction can be made in the tyrosinase gene so that it results in the development of pigmented hairs at the treated locations of an animal skin.

The Examiner also avers that in light of the teachings in the Alexeev reference, there would have been a reasonable expectation of success in carrying out the claimed method. Applicant respectfully disagrees and submits that there is no reasonable expectation of success from the Alexeev's report, which merely demonstrates the ability of the Tyr A RNA-DNA polynucleotide to correct tyrosinase gene in melan-c cells *in vitro* and does not establish a correlation to an intact skin situation. More specifically, there is no reasonable expectation of success given the scarcity of melanocytes, which account for only a minor portion (1%) of the total population of cells present in skin of a mammal, and hair cycle dependent expression of tyrosinase in the skin coupled with other issues such as, for example, hair pigmentation may require correction of many melanocytes per hair follicle to produce and deposit enough melanin in hair shaft, the gene correction of tyrosinase gene in one or two melanocytes per hair follicle

[1] It is well established that "obvious to try" is improper consideration in adjudicating obviousness issue. *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988).

may not be detected as a phenotypic change and the absence of any guidance in the cited references for the stable correction of tyrosinase gene in skin cells *in vivo*.

Further, the cited art does not provide any guidance on how to cause stable genetic correction in the tyrosinase gene in skin cells by using a Tyr-A RNA-DNA oligonucleotide such that phenotypic changes are seen over a period of time lasting for more than one hair cycle. In the absence of such guidance in the cited art, there is no reasonable expectation of success.

In essence, there are no teachings in Yoon, Alexeev, Furth, Gilchrest and Stout references to suggest the desirability, and thus obviousness, of combining these references in a way that would lead one to the claimed method. There is no reasonable expectation of success. Applicant respectfully submits that the cited combination of references is nothing more than an indiscriminate combination of prior art references in an attempt to reconstruct the claimed invention by hindsight.[2]

In response to the Examiner's assertions on pages 7-10 of the Office Action, Applicant respectfully submits the following:

The Examiner makes a statement that "[s]ince the polynucleotide disclosed in the present specification is the same as that disclosed in the art, any method [in vitro or in vivo or ex vivo] using the TyrA RNA DNA polynucleotide would result in the same outcome." Applicant respectfully submits that it is a statement without support , factual or otherwise.

The Examiner avers that "reliance upon inherency is not improper" and cites *In re Skoner,* et al. 186 USPQ 80 (CCPA). The Examiner's reliance on *Skoner* in support of the present obviousness rejection appears to be misplaced and unwarranted. In *Skoner*, the rejection involved only one prior art reference (not a combination of prior art references as in the present case) and the issue revolved around the extent of brushing to improve adhesion. The court, while acknowledging that the rejection should have been founded upon § 102 instead of § 103, noted that the prior art reference disclosed wire brushing in an attempt to achieve an improved adhesion like those of the appellants therein. Further, the court found that the extent of wire brushing carried out by the prior art reference to be inherently the same as that of the appellants and,

[2] Use of hindsight in the selection of references to establish a case of obviousness is improper. *In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998).

therefore, the rejection was proper. In the present case, in contrast, the Alexeev reference relates to gene correction in *in vitro* cultured cells and teaches or suggests nothing about the correction of a tyrosinase gene in cells of a mammalian skin in vivo as claimed. Inherency requires that the missing descriptive material is "necessarily present," not merely probably or possibly present in the prior art. The Examiner has not established that the missing descriptive material is "necessarily present," in the cited art. Further, "[t]hat which may be inherent is not necessarily known. *In re Newell*, 13 USPQ2d 1248 (Fed. Cir. 1989). Obviousness cannot be predicated on what is unknown and to establish that a given combination would have been obvious, there must be supporting teaching in the prior art.

The Examiner also seems to indicate that the *Papesch* doctrine applied in *Chupp* would not apply in the present case but the *Papesch* doctrine applied in *Albrecht* would apply and quotes that "[o]ur position is that from the standpoint of patent law a compound and all of its properties are inseparable (page 589)." Applicant believes that the Examiner's method of analysis is founded on legal error because it sidesteps the fact-intensive inquiry mandated by § 103. In other words there are not *Albrecht* obviousness rejections or *Chupp* obviousness rejections but rather only § 103 obviousness rejections.

Further, the Examiner's quotation would be relevant if the claims at issue in the present case were to be composition claims involving the use of Tyr-A RNA-DNA oligonucleotide for correction of mutated genes in melanocyte cell cultures. See, MPEP § 2112.01 where it quotes that "[a] chemical composition and its properties are inseparable." The claims at issue are process (35 U.S.C. §100 (b)) claims not the composition claims and, therefore, the rejection should address the process claims. To the extent that the Examiner asserts that "since the TyrA RNA-DNA disclosed in the specification and the prior art is the same, any property or affect of using the product would be expected," in a process using the Tyr-A RNA-DNA, Applicant respectfully submits that it is an assertion without support.

Furthermore, the Examiner seems to infer that the *Papesch* doctrine applied in *Chupp* would apply to the processes claims that are similar but not identical. As pointed above, the prior art process relates to gene modifications in isolated and cultured melan-c cells using a Tyr-A RNA-DNA oligonucleotide but not to a process of correcting a mutation in a tyrosinase gene

in cells a mammalian skin in vivo using a Tyr-A RNA-DNA oligonucleotide. It is not the case where the prior art discloses a method of correcting a mutation in a gene other than tyrosinase gene in cells of a mammalian skin in vivo using a Tyr-A RNA-DNA oligonucleotide in order for the prior art disclosure to be similar to the claimed process. One of ordinary skill in the art would readily recognize that an *in vitro* process is not similar to an *in vivo* process, much less being the same. Therefore, the *Papesch* doctrine applied in *Chupp* should apply.

As to the reliance on "*In re* Dill, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979)" Applicant respectfully believes that the Examiner incorrectly drew from *Dill,* a case turning on specific facts, to reject claims on the ground that "claim 40 is very broad encompassing any method of delivery and does not recite the specific parameters used to obtain the result indicated as `surprising'." In *Dill*, the patentee offered "no proof whatsoever pertaining to unexpected results obtained with the invention" at issue therein. That is not the case here. The Examiner concedes that the Applicant pointed to certain unexpected results but contends that claims are "not specifically drawn to the unexpected result pointed to by Applicant." Further, the assertion that "claim 40 is very broad" is improper for a § 103 determination. *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987); *Burlington Indsustries, Inc., v. Quigg*, 3 USPQ2d 1436 (Fed. Cir. 1987).

The Examiner further asserts on page 9 of the Office Action that "the number of cells or area assayed is not clearly set forth." Applicant respectfully disagrees and requests the Examiner's attention to page 37, lines 23-25 of the specification where it states that "[a]nimals were sacrificed at 2-5 months after birth and skin biopsies (5 mm^2) were taken from both treated and untreated areas." The specification, for example, at page 15, lines 7-9 states that "[s]urprisingly, a high level of gene correction approaching 40% was observed from skin biopsy of animal, in which RDO was injected intradermally or topically applied." A person of ordinary skill in the art would know how to determine the number of cells and the % gene correction based on the area of the skin assayed after a given treatment.

Finally, the Examiner concludes, on page 10 of the Office Action that "the specification fails to provide a clear and adequate description of the specific experiments performed or relied upon in Applicants arguments." Applicant respectfully disagrees and submits that the

specification provides more than sufficient teachings relied upon by the Applicant in its rebuttal of the *prima facie* obviousness rejection. See, page 12, line 5 through page 16, line 20 of the specification. As is apparent from the teachings in the specification, Applicant's disclosure contributes something unobvious to the knowledge in this art and that its claims are fully commensurate in scope with that contribution. Further, it is that the specification not the claims should contain specific data supporting the advantages of the claimed invention. *In re Soni;* See also the Examiner's notation on page 8 of the Final Office Action of July 31, 2002. This is true even of the unexpected advantages that an Applicant may rely upon to rebut a *prima facie* case of obviousness. *In re Soni,* 34 USPQ 2d 1684 (Fed. Cir. 1995); *In re Chupp*, 2 USPQ2d 1437 (Fed. Cir. 1987); and *In re Albrecht*, 185 USPQ 585 (CCPA 1975).

Accordingly, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of claims 40-42 under 35 U.S.C. § 103(a). Even if *prima facie* obviousness has been established, which it has not, it is urged that the cited art nonetheless fails to render the present invention obvious under a proper § 103 analysis as discussed above.

III. Obviousness-Type Double Patenting Rejection

Claims 40-42 stood provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 8, 16-18 of copending Application No. 09/962,628. This rejection is respectfully traversed.

First, the lengthy double patenting rejection, spanning pages 11-13, of the Office Action is rather ambiguous. For example, it refers to certain claims of the U.S. Patent 5,166,065. Further, in view of the fact that the present claims are distinguishable from claims 1, 2, 8, 16-18 of the copending Application No. 09/962,628, and further in view of the fact that allowability of the present claims has not yet been acknowledged, Applicant believes it is premature to file a Terminal Disclaimer at this time.

Accordingly, withdrawal of this rejection is respectfully requested.

IV. New claims 43-53

New claims 43-53 , directed to a non-human animal model having a skin disorder, have been added. These new claims substantially correspond to the previously canceled clams 32-39.

The skin disorder in the claimed animal model is a result of mutations induced in genes of skin cells (which are somatic cells, not germ cells) by using a RNA-DNA oligonucleotide and These animal models are incapable of germline transmission of the mutated gene. Applicant respectfully submits that the cited references do not disclose or teach the non-human animal model recited in these new claims. Therefore, the cited references cannot anticipate the new claims. Further, the cited references, neither alone nor in combination teach or suggest the claimed non-human animal model. Therefore, these references cannot render the new claims obvious.

V. Conclusion

Applicant believes this response to be a full and complete response to the Office Action. Accordingly, favorable reconsideration in view of this response and allowance of all of the pending claims are earnestly solicited.

Respectfully submitted,

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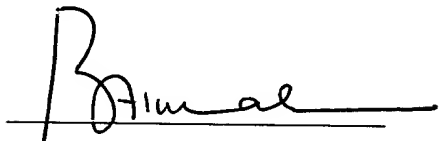

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